Remarks

I. Support for Amendments

The foregoing amendments to the specification are sought to update and correct the priority information for the present application (specifically, to provide the patent numbers or abandonment status for certain related applications, and to delete a duplicate cross-reference). Hence, these amendments to the specification do not add new matter.

Support for the foregoing amendments to the claims may be found throughout the specification. Specifically, support for new claims 30-43 may be found in the specification at pages 11-14, at pages 25-26, at pages 33-34, and throughout the Examples and the drawings; and support for the amendments to claim 16 may be found in the specification at pages 11-14, at page 26, at page 32, lines 9-12, and at page 33, lines 5-15. Accordingly, these amendments to the specification and claims do not add new matter, and their entry and consideration are respectfully requested.

II. Status of the Claims

By the foregoing amendments, claims 1-13, 21-26, 28 and 29 have been cancelled without prejudice or disclaimer as being drawn to subject matter restricted into a non-elected restriction group in the present application; new claims 30-43 are sought to be entered; and claim 16 has been amended. These amendments do not add new matter. Upon entry of the foregoing amendments, claims 14-20, 27 and 30-43 are pending in the present application, with claims 14 and 16 being the independent claims.

III. Summary of the Office Action

In the Office Action dated July 17, 2001, the Examiner has requested clarification of one portion of the specification, and has made two rejections of the claims. Applicants respectfully offer the following remarks to overcome or traverse each element of this rejection in the Office Action.

IV. The Priority Claim

As an initial matter, the Examiner contends that the priority claim in the present specification, required under 37 C.F.R. § 1.78 is unclear for reciting "a lot of related applications." *See* Paper No. 8 at page 2, section 2. Applicants note that the first sentence of the cross reference section appearing at page 1 of the specification makes it quite clear that "[t]he present application claims the benefit of U.S. Provisional Application No. 60/161,403, filed October 25, 1999." Hence, the 35 U.S.C. § 119 priority application for the present application is clearly identified in the first sentence of the specification, in compliance with 37 C.F.R. § 1.78. The remaining applications listed in the cross-reference section are *related* applications, to which priority has not been claimed in the present application. Applicants note that such cross-references are permitted under 37 C.F.R. § 1.78(a)(2) ("Cross references to other related [*i.e.*, non-priority] applications may be made when appropriate (see § 1.14)."). Hence, it is respectfully believed that the present specification fully complies with the requirements of 37 C.F.R. § 1.78.

V. The Rejection Under 35 U.S.C. § 102(b) Over Stemmer

In the Office Action at pages 2-4, the Examiner has rejected claims 14-20 and 27 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,605,793 (Doc. "A" cited on the Form PTO-892 attached to Paper No. 8; hereinafter "Stemmer"). Applicants respectfully traverse this rejection.

In making this rejection, the Examiner extensively characterizes the methods disclosed in Stemmer (*see* Paper No. 8 at pages 3-4), concluding that "Stemmer teaches all limitations recited by claims 14-20 and 27." Paper No. 8 at Page 4, section 5, final sentence. Applicants respectfully disagree. The cloning methods disclosed in Stemmer rely on an initial restriction digestion of the target and transferred nucleic acid molecules, followed by homologous recombination via traditional crossing-over. *See* Stemmer at col. 5, lines 59-64; at col. 6, lines 24-26; at col. 7, lines 6-8; in Figure 1; and in claim 1. In contrast, independent claims 14 and 16, and hence the remaining claims that depend therefrom, are drawn to methods for cloning nucleic acid molecules or populations thereof by recombination using recombination sites, *without* the use of restriction digestion and ligation followed by homologous recombination as in Stemmer. The cloning methods of claims 14 and 16, then, differ distinctly from the restriction cloning methods disclosed in Stemmer. Thus, Stemmer does *not* disclose the use of "recombinational cloning" as that term is defined in the present specification.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). In addition, a claim can only be anticipated by a publication if the publication describes the claimed invention with sufficient enabling detail to place the public in possession of the invention. *See In re*

Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). Since Stemmer patent does not expressly or inherently disclose, in an enabling fashion, methods for transferring nucleic acid molecules into vectors via recombinational cloning, this reference cannot and does not anticipate claims 14-20 and 27 as currently presented. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Stemmer are respectfully requested.

VI. The Rejection Under 35 U.S.C. § 102(b) Over Atlung

In the Office Action at pages 4-5, the Examiner has rejected claims 16-20 and 27 under 35 U.S.C. § 102(b) as allegedly being anticipated by Atlung *et al.*, *Gene 107*:11-17 (1991) (Doc. AT4, of record; also cited as Doc. "U" on the Form PTO-892 attached to Paper No. 8; hereinafter "Atlung"). Applicants respectfully traverse this rejection.

As an initial matter, Applicants respectfully disagree with the Examiner's contention that "ligation sites could be considered as first and second recombination sites as described in claim 16." Paper No. 8 at page 5, lines 8-9. The present specification makes it quite clear that standard ligation sites (*i.e.*, sites at which nucleic acid molecules are to be joined by ligase enzymes in traditional restriction cloning methods) are *not* considered recombination sites in accordance with the present invention:

> Site-specific recombinases are proteins that are present in many organisms (e.g. viruses and bacteria) and have been characterized as having both endonuclease and ligase properties. These recombinases (along with associated proteins in some cases) recognize specific sequences of bases in DNA and exchange the DNA segments flanking those segments. The

> recombinases and associated proteins are collectively referred to as "recombination proteins" (see, e.g., Landy, A., *Current Opinion in Biotechnology* 3:699-707 (1993)).
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> A key feature of the recombination reactions mediated by the above-noted recombination proteins are recognition sequences, often termed "recombination sites," on the DNA molecules participating in the recombination reactions. These recombination sites are discrete sections or segments of DNA on the participating nucleic acid molecules that are recognized and bound by the recombination proteins during recombination.

Specification at page 2, lines 3-9, and at page 4, lines 15-20. Hence, ligation sites (or, more accurately, restriction sites) do not qualify as "recombination sites," since the ligase enzyme that binds ligation sites (or the restriction enzyme that cleaves at restriction sites) does not "have both endonuclease and ligase properties" and does not "exchange DNA segments." This is not to say, of course, that ligation sites cannot *comprise* one or more recombination sites, or that recombination sites as defined in accordance with the present invention cannot be located at or near the termini of linear or nicked circular nucleic acid molecules. The point here is simply that the restriction (or ligation) sites described in Atlung cannot be considered as recombination sites. Hence, the Examiner's above-noted contention that ligation sites could be considered as first and second recombination sites as described in claim 16 is incorrect.

Secondly, Atlung fails to disclose the use of nucleic acid molecules comprising at least two (*i.e.*, at least a first and a second) recombination sites on a single nucleic acid molecule, which are then recombined (although not necessarily with each other) via recombinational cloning. The reaction depicted in Atlung in Figure 2A at page 14, and referred to by the Examiner in making this rejection, is a reaction between a single *att*P site on a *lac*Z fusion plasmid and a single *att*B site on an *E. coli* chromosome. Hence, this reaction is between *two* nucleic acid molecules each containing *one* recombination site, not a reaction involving two

recombination sites on the *same* nucleic acid molecule. Claim 16 clearly specifies that the recombinational cloning reaction involves at least a first and a second recombination sites (*i.e.*, at least two recombination sites) on "a" (*i.e.*, on the same) nucleic acid molecule. Thus, Atlung does not disclose all of the elements of claim 16.

Since Atlung does not expressly or inherently disclose methods of recombinational cloning involving at least two recombination sites on a single nucleic acid molecule, this reference cannot and does not anticipate the claims as currently presented under *Kalman*, *Donohue* and *PPG Industries*. Accordingly, reconsideration and withdrawal of the rejection of claims 16-20 and 27 under 35 U.S.C. § 102(b) over Atlung are respectfully requested.

VII. Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the outstanding rejections.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt entry and favorable consideration of the foregoing amendments and remarks, and allowance of all pending claims, are earnestly solicited.

Respectfully submitted,

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Version with markings to show changes made

In the Specification:

In the specification at page 1, the cross-reference section appearing at lines 7-17 is amended as follows:

The present application claims the benefit of U.S. Provisional Application No. 60/161,403, filed October 25, 1999. The present application is also related to U.S. Appl. No. 08/486,139, filed June 7, 1995 (now abandoned), U.S. Appl. No. 08/663,002, filed June 7, 1996 (now U.S. Patent No. 5,888,732), U.S. Appl. No. 09/177,387 filed October 23, 1998, U.S. Appl. No. 09/296,280, filed April 22, 1999 (now U.S. Patent No. 6,277,608), U.S. Appl. No. 09/517,466, filed March 2, 2000, U.S. Appl. No. 09/518,188, filed March 2, 2000, U.S. Appl. No. 09/438,358, filed November 12, 1999, U.S. Appl. [Nos. 09/296,280 and] No. 09/296,281, [both] filed April 22, 1999 (now abandoned), U.S. Appl. No. 09/005,476, filed January 12, 1998 (now U.S. Patent No. 6,171,861), and U.S. Appl. Nos. 09/233,492 and 09/233,493, both filed January 20, 1999 (now U.S. Patent Nos. 6,270,969 and 6,143,557, respectively), the disclosures of which applications are entirely incorporated herein by reference.

In the Claims:

(a) Claims 1-13, 21-26, 28 and 29 are cancelled without prejudice or disclaimer.

(b) New claims 30-43 are sought to be entered.

(c) Claim 16 is amended as follows:

16. (Once amended) A method for [cloning] producing a nucleic acid molecule or a population of nucleic acid molecules comprising:

inserting one or more integration sequences each comprising at least one recombination site into at least one nucleic acid molecule thereby [resulting in said] producing a nucleic acid molecule comprising at least a first and a second recombination site; and

causing said at least first and second recombination sites to recombine via a recombinational cloning reaction.